REMARKS

Claims 29-54 are pending in the subject application. The Examiner has withdrawn claims 34, 35, 40, 41, 47, 48, 53 and 54 from further consideration. Applicant has not amended, added or cancelled any claims. Accordingly, claims 29-33, 36-39, 42-46 and 49-52 are pending and under examination. Applicant has hereinabove amended the specification. These amendments were made in response to the Examiner's objections set forth below. Applicant contends that these amendments do not present any issue of new matter. Therefore, entry of this Amendment is respectfully requested.

In view of the arguments set forth below, applicant maintains that the Examiner's rejections have been overcome and respectfully requests that the Examiner reconsider and withdraw same.

Information Disclosure Statement

The Examiner stated that applicant's Information Disclosure Statements (IDS) filed December 11, 2003 and September 13, 2004 have each been received and entered into the application. The Examiner stated that as reflected by the completed copies of form PTO-1449 (11 pages total) included with the June 20, 2006 Office Action, the Examiner has considered the cited references, with the exception of the Limatta et al. reference cited at page 5 of the IDS filed December 11, 2003. The Examiner stated that this reference could not be located after a reasonable search by the Examiner and was, therefore, not considered.

In response, applicant respectfully traverses. Applicant notes that Limatta et al. (1994) was mistakenly cited as having been submitted with an Information Disclosure Statement filed in connection with U.S. Serial No. 09/104,880, filed June 25, 1998. However, Limatta et al. was first cited by the Examiner in a June 6, 2000 Office Action issued in connection with U.S. Serial No. 09/104,880. Therefore, pursuant to 37 C.F.R. §1.98(d) a copy of Limatta et al. is not required since it was previously cited by the United States Patent and Trademark Office in an earlier application relied on for an earlier effective filing date. Nevertheless, applicant without conceding the correctness of the Examiner's assertion and to expedite prosecution of the subject application, attaches hereto as **Exhibit F** a copy of the Limatta et al. reference, which is listed on Form PTO-1449 attached hereto as **Exhibit G**, for consideration by the Examiner.

Applicant respectfully requests consideration of the above-identified reference and that this reference be printed on any patent which issues from the subject application.

May 3, 2004 Preliminary Amendment

The Examiner stated that applicant's Preliminary Amendment filed May 3, 2004 has been considered, but the amendment made to page 13 of the specification at lines 1-14 fails to comply with the standards set forth in 37 C.F.R. §1.121(b)(1)(ii) regarding the manner and form of amendments. The Examiner stated that in particular, it is noted that the amendment at page 13, lines 1-14, fails to set forth the entire full text of the paragraph to be amended. The Examiner stated that

applicant has only set forth the text of the portion of the paragraph that appears at page 13. The Examiner stated that in order to comply with 37 C.F.R. 1.121(b)(1)(ii), the full text of the paragraph as it begins at page 12, line 17, and ends at page 13, line 14, should be set forth as the full text of the paragraph to be amended with the appropriate mark-up to indicate what has been changed. The Examiner stated that appropriate correction to the amendment for compliance with 37 C.F.R. 1.121(b)(1)(ii) should be made and resubmitted to the Office for consideration.

In response, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's objection and to expedite prosecution of the subject application, has hereinabove included the entire paragraph at page 10, line 12, by deleting the alterations objected to by the Examiner. Therefore, the Examiner's objection is now moot. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of objection.

Requirement for Restriction/Election

Applicant hereby acknowledges the Examiner's withdrawal of the requirement for election and statement that the inventions of Groups I-IV will be examined together.

Objection to the Specification

The Examiner objected to the application because of alterations which have not been initialed and/or dated as is required by 37 CFR §1.52(c). The Examiner directed applicant's

attention specifically to the changes made at page 10, line 12, of the present specification.

In response, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's objection and to expedite prosecution of the subject application, has hereinabove provided the entire amended paragraph, which begins on page 12, line 17, and ends at page 13, line 14. Therefore, the Examiner's objection is now moot. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of objection.

Claim Rejections Under 35 U.S.C. §103

The Examiner has rejected claim 29-33, 36-39, 42-46 and 49-52 under 35 U.S.C. §103(a) as being unpatentable over Bar-Tana et al. (*New Antidiabetic Drugs* (1990)) in view of Hertz et al. (*JBC* (1995)), and Ferrannini et al. (*Diabetologia* (1991)).

According to the Examiner, Bar-Tana teaches the administration of MEDICA 16 (hereafter M16) to rats, for a 50-70% decrease in plasma triacylglycerol, 40-50% decrease in plasma cholesterol and a corresponding 1.5-fold increase in HDL-cholesterol (VLDL+LDL)-cholesterol ratio, when treated orally.

The Examiner stated that the difference between Bar-Tana (1990) and the presently claimed subject matter is that the reference fails to teach treatment of dyslipoproteinemia, or administration of M16 to a human subject.

The Examiner stated that these differences between claimed

subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time of the invention, because it would have been *prima facie* obvious that a therapeutic agent that has already shown efficacy in reducing plasma triglycerides and plasma cholesterol would necessarily have been suggestive of the same level of efficacy in treating the disorder of dyslipoprpteinemia, defined in the claims as combined hypertriglyceridemia and hypercholesterolemia. The Examiner stated that one of skill in the art would have likely been motivated to administer the compound M16 to a subject having combined hypertriglyceridemia and hyperchleterolemia because the compound was known to reduce plasma levels of both triglycerides and cholesterol such that one of ordinary skill in the art would have reasonably expected success in treating a condition characterized by abnormally elevated levels of both triglycerides and cholesterol.

In response to the Examiner's rejection, applicant respectfully traverses and maintains that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Applicant contends that the references cited against the rejected claims fail to support a *prima facie* case of obviousness because one of ordinary skill would not have been motivated to combine the teachings of the cited references at the time of the invention.

Claim 29 is directed to a method for the treatment of humans suffering from Syndrome X a syndrome comprising some or all of

dyslipoproteinemia (combined hypertriglyceridemia/hyperchlesterolemia/low HDL-cholesterol), obesity, impaired glucose tolerance leading to noninsulin-dependent diabetes (NIDD), hypertension and thrombogenic/fibrinolytic defects (see the paragraph bridging pages 9-10 of the specification) (emphasis added).

Bar-Tana et al. (1990) is an academic study, discussing the hypolipidemic effects of M16 in normal and nephrotic **rats**, not in humans (emphasis added). The treatment of normal as well as nephrotic rats with M16 resulted in an acute reversible inhibition of liver lipogenesis and cholesterogenesis with a hypolipidemic effect which was sustained as long as the drug was administered.

Contrary to the Examiner's assertion, it is respectfully submitted that one of skill in the art would not have expected the results from animals, specifically rats, to be predictive of results in a human, as will be detailed below. In addition, it should be noted that claim 29 is not directed to the treatment of mere hyper-triglyceridemia or hypercholesterolemia, but to the treatment of Syndrome X in humans, which is not described in the Bar-Tana reference. The nephrotic rat of Bar-Tana and its response to M16 is not predictive for human dyslipoproteinemia for the following reasons:

a. A rat cannot serve as a model for human lipoproteins profile and metabolism even before it is artificially induced with nephrosis. In contrast to normolipemic humans, considered to represent an LDL-

cholesterol species, where cholesterol distribution is roughly 70% LDL, 10% VLDL and 20% HDL, in the normolipemic rat there is practically no LDL-cholesterol, as can be seen, e.g. from Table 1 of Bar-Tana (only 1.6% LDL-cholesterol). Therefore, rat lipoprotein profile and metabolism do not simulate the human case.

b. The nephrotic dyslipoproteinemia in rats has nothing to do with the human disease, and therefore cannot serve as a model for dyslipoproteinemic human patients (let alone for the claimed Syndrome X, of which dyslipoproteinemia is not necessarily an essential pathology). This animal is induced with nephrosis by PAN (puromycin aminonucleoside). This agent damages the kidney, causing albuminuria, and as a result, the liver begins to over-synthesize albumin, including lipoproteins, for the sake of maintaining blood osmotic pressure in the face of massive protein loss in the urine. This has nothing to do with human dyslipoproteinemia. Therefore, modulating this specific condition in the nephrotic rat by M16 does not predict its effect in human dyslipoproteinemia. For example, if M16 could prevent or cure the kidney damage, it would have had the same lipid lowering effect in the PAN nephrotic rat, without any relevance to affecting the state of lipoproteins in human dyslipoproteinemia.

Therefore, the rat is not a suitable animal model, neither is the specific nephrotic rat, for

dyslipoproteinemia in humans.

c. The apparent decrease in HDL-cholesterol percentage in the nephrotic rat (to which the Examiner refers on page 7 of the Office Action) just reflects the robust increase in the VLDL- and LDL-cholesterol species. However, the absolute concentration of HDL-cholesterol is massively increased by PAN nephrosis in the rat (from 30.4 [Bar-Tana et al. Table 1] to 121.8 [Table 3]). This is in contrast to the low HDL-cholesterol in human dyslipoproteinemia, defined by the decrease in absolute concentration of plasma HDL-cholesterol and not by the relative share of HDL-cholesterol in total cholesterol. In addition, it may be mentioned that according to the American ATPIII (Adult Treatment Panel III) only the plasma levels of HDL-cholesterol are important, never the relative part of HDL-cholesterol in total cholesterol.

d. The effect of M16 on HDL-cholesterol in the normolipemic or nephrotic rat is contrary to, and could not predict, its therapeutic effect in humans. As can be seen in Table 1 of Bar-Tana et al., treatment of normal rats with M16, lowered HDL levels (from 30.4 to 20.6), and in the nephrotic rats of Table 3, there was almost no change between treated and non-treated rats. That is in contrast to increasing HDL-cholesterol in human dyslipoproteinemic patients, as proved by applicant's clinical trials in humans, further

discussed below.

Therefore, because of the irrelevance of this animal model to human dyslipoproteinemia, and in light of the lack of positive effect of M16 on HDL-cholesterol in this animal model, one of skill in the art could not have predicted the effect of M16 in humans in light of its effect in PAN nephrotic rats.

Hertz et al., cited by the Examiner, does not remedy the deficiencies of Bar-Tana.

Hertz et al. illustrates (see Fig. 6) the two pathways for suppression of HNF-4α-responsive genes (e.g., apolipoprotein C-III which is responsible for the clearance of plasma triglycerides-rich lipoproteins) by amphipathic carboxylic peroxisome proliferators (PP)/PPARα ligands like the compounds used in the present application. The indirect pathway is through activation of PPARα/RXRα by the free PP acid and is mediated by HNF-4α displacement of its cognate enhancer by binding of PP-activated PPARα/RXR under conditions where PPARα is transcriptionally non-productive, while the direct pathway requires the respective CoA thioesters (PP-CoA) and is mediated by PP-CoA inhibition of the transcriptional activity of HNF-4α. Thus, the direct mechanism results in inhibition of HNF-4α by PP-CoA independently of PPARα. The PPARα-independent effect of PP-CoA is further exemplified by realizing that in contrast to free amphipathic carboxylic acids which activate PPARα (see Hertz, R. et al., *Eur. J. Biochem.* 221: 611-615 (1994), **Exhibit A**), PP-CoAs do inhibit its transcriptional activity (see Elholm, J. et al., *J. Biol. Chem.* 276: 21410-21416 (2001), **Exhibit B**).

Therefore, for achieving the desired hypolipidemic effects in humans independently of PPARα, only compounds which can endogenously form thioesters with CoA, as those claimed in the present application, can be used. Compounds which do not form thioesters with CoA, like Cl-DICA (2,2,13,13,-tetrachloro-tetradecane-1,14-dioic acid), are inefficient as direct suppressors of HNF-4α, and therefore as hypolipidemic agents in humans (see Exhibit A, e.g. Figure 7, and the paragraph bridging pp. 1061-1062).

It was not known before applicant's filing date, that only compounds that can form a thioester with CoA are useful in the treatment of humans. Interestingly, these active agents which endogenously form a thioester with CoA act, as described in the specification, independently of PPARα activation (see for example, lines 3-4, page 14 and Example 4 of the subject specification).

It is to be emphasized, that since the application was filed, clinical trials in human patients were conducted. These trials showed that M16, which is capable of yielding endogenously the respective CoA thioester, is indeed effective in humans in lowering plasma lipids (see **Exhibit C**). This is in contrast to Cl-DICA, which is incapable of yielding the respective CoA thioester endogenously (see **Exhibit A**) and which appears to be ineffective in humans, in spite of its efficacy in rodents (results of clinical trials in **Exhibit D**).

It is now known that the finding that some xenobiotic compounds, e.g. M16 and Cl-DICA, had a hypolipidemic effect in

rats, could not lead one of skill in the art to the conclusion that they would also be active in other animals, let alone in humans.

Indeed, as found by Mayorek et al. (*Biochem. J.* (1993) 289: 911-917, **Exhibit E**), M16 did not exhibit any hypotriglyceridemic effect in hamsters, in spite of the fact that the hamsters' lipoprotein metabolism, their plasma lipoproteins profile, and their response to dietary fat are considered to closely resemble those of humans (see, e.g. Liu, GL, et al., *Comp. Biochem. Physiol.* A 99, 223-228, (1991); Chapman MJ et al., *J. Lipid. Res.* 34, 943-959 (1993); Sullivan MP, et al., *Lab Anim Sci* 43, 575-578 (1993); Hoang V, et al., *Biochim Biophys Acta* 1254, 37-44 (1995); Ohtani H, *J Lipid Res.* 31. 1413-1422 (1990), copies of which may be provided). Hence, in fact, the prior art teaches away from the invention, and one of skill in the art would have been deterred from even trying in humans compounds that were ineffective in hamsters.

Therefore, the hypolipidemic, particularly hypotriglyceridemic, effect in humans was surprising, especially in view of the lack of any effect of Cl-DICA, which was very potent in rats, and the lack of M16 effect in hamsters.

The hypolipidemic activity in claim 29 is indicated for Syndrome X, which comprises, *inter alia*, <u>combined</u> hypertriglyceridemia/hyperchlesterolemia/low HDL-cholesterol which, in contrast to non-specified dyslipoproteinemia, is specifically characteristic of Syndrome X (see e.g. Solymoss BC et al., *Am J Cardiol* 76, 1152-1156 (1995)). Moreover, so

far as hypertriglyceridemia (as part of Syndrome X) is concerned, the claim is directed to the treatment of a syndrome (dyslipoproteinemia), characterized by the presence of all said three symptomatic conditions. There is no reason to assume that medicaments that in some situations can alleviate one or two of the symptoms would be relevant to the specific syndrome combining all three.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 29-33, 36-39, 42-46 and 49-52 over these references.

In view of the above remarks, applicant maintains that claims 29-33, 36-39, 42-46 and 49-52 satisfy the requirements of 35 U.S.C. §103(a) and respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Obviousness-Type Double Patenting Rejection

Provisional Rejection

The Examiner provisionally rejected claims 36-39, 42-46 and 49-52 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 29-34 of copending U.S. Patent Application No. 10/735,452.

In response, applicant respectfully requests that this rejection be held in abeyance until all other grounds of rejection of the pending claims have been overcome.

Non-Provisional Rejections

U.S. Patent No. 4,689,344 in view of Bar-Tana

The Examiner rejected claims 36-39, 42-46 and 49-52 over claims 5 and 19 of U.S. Patent No. 4,689,344 (the '344 patent) in view of Bar-Tana (Bar-Tana et al., New Antidiabetic Drugs, 1990) under the judicially created doctrine of obviousness-type double patenting. The Examiner asserted that although the conflicting claims are not identical, they are not considered to be patentably distinct.

The Examiner stated as follows: (i) the patented claims teach administration of M16 to a patient for reducing serum cholesterol; and (ii) Bar-Tana teaches that administration of M16 was known in the art to reduce plasma triglycerides, as well as cholesterol, as well as to increase HDL/(VLDL + LDL) cholesterol ratio.

In light of such, the Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention that the administration of M16 to identical hosts would have necessarily resulted in the reduction of serum triglycerides and an increase of dHDL/(VLDL + LDL) cholesterol ratio, regardless of whether such properties of the compound had been recognized by the patentee at the time of the invention.

In response, applicant respectfully traverses.

Applicant's invention now claimed in the subject application provides methods of (a) treating dislipoproteinemia (claim

36), (b) lowering plasma levels of triglycerides (claim 42), and (c) increasing plasma levels of HDL cholesterol, in a human subject. Claims 36, 42 and 49 of the subject application recite methods for treating humans. However, Bar-Tana describes experiments with nephrotic rats, as detailed in applicant's arguments set forth hereinabove. Even if relating to the example in the '344 patent, contrary to what the Examiner states, the hosts are not identical, because the patent describes experiments with rats, not nephrotic rats, and with *Psamonys obesus*. Thus, even these two publications use different hosts, not humans, as claimed in the present application. Accordingly, the Examiner has incorrectly asserted that applicant's claimed invention and the claims of the '344 patent in view of Bar-Tana describe the "same compound to the same animal."

In addition, applicant notes that claim 5 of the '344 patent is directed to a pharmaceutical composition comprising at least one compound selected from a group including M16 while claims 36, 42 and 49 of the subject application are directed to methods for treating a subject. Therefore, claims 36, 42 and 49 of the subject application cannot be identical nor obvious over claim 5 of the '344 patent since the claims are directed to distinct subject matter, i.e. a pharmaceutical composition and a method, respectively.

Furthermore, claim 19 of the '344 patent is directed to a method for reducing serum cholesterol in a subject while the claims of the subject application are directed to methods of (a) treating dislipoproteinemia (claim 36), (b) lowering plasma levels of triglycerides (claim 42), and (c) increasing

plasma levels of HDL cholesterol, in a human subject. Applicant contends that "treating dislipoproteinemia", "lowering levels of triglycerides" and "increasing levels of HDL cholesterol" are not the same nor would they have been obvious over claim 19 of the '344 patent which recites "reducing serum cholesterol".

The combination of these different features is clearly unobvious from the combination of the corresponding elements recited in any of claims 5 or 19 of the '344 patent. Applicant further notes that in the comparison of patented claim to pending claim required for obviousness-type double patenting, only individual claims of the patent may be considered. Thus, the claims of the patent may not be combined like prior art for this purpose. Only the specific combination of these elements as now recited provides the unexpected benefits associated with applicant's claimed invention. Accordingly, applicant maintains that claims 36-39, 42-46 and 49-52 are patentably distinct over claims 5 and 19 of the '344 patent.

In view of the above remarks, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

U.S. Patent No. 6,303,653

The Examiner rejected claims 29-33 over claims 1-3 and 8 of U.S. Patent No. 6,303,653 (the '653 patent) under the judicially created doctrine of obviousness-type double patenting.

In response, applicant respectfully traverses.

The claims of the '653 patent are directed to a method of treating an HNF-4 mediated disease state which method comprises administering a therapeutically effective amount of a compound which inhibits HNF-4 controlled transcription independently of PPARα activation (claim 1), wherein said compound comprises an amphipathic carboxylate convertible to its respective CoA thioester (claim 2), wherein said amphipathic carboxylate is a xenobiotic amphipathic carboxylate (claim 3), for the treatment of Syndrome X (claim 8).

The claims of the subject application are directed to a method for the treatment of Syndrome X which comprises administering to a human subject a therapeutically effective amount of a xenobiotic fatty (claims 29-32).

Applicant notes that Syndrome X characteristics mediated by HNF-4a only comprise a partial group of the Syndrome's phenotype because:

a. Syndrome X phenotype is determined by the interplay of organs that do express HNF-4a (e.g., liver, pancreas), as well as organs that lack HNF-4a (e.g., skeletal muscle, adipose tissue) but still play a dominant role in the Syndrome context; and

b. HNF-4a is not the only etiological factor that determines the Syndrome phenotype in HNF-4a expressing organs. In these organs the phenotype is determined by the interplay of HNF-4a with other etiological factors

(e.g, AMP-activated protein kinase (AMPK)).

Thus, methods of treating Syndrome X by merely modulating HNF-4a activity would be limited to treating hepatic and pancreatic aspects of the Syndrome (e.g., dyslipoproteinemia, insulin secretion), while falling short of treating the Syndrome in the muscle and adipose context (e.g., insulin resistance, adipose cytokines). Moreover, merely modulating HNF-4a activity as claimed in the '653 patent may result in incomplete treatment. Hence, methods of treating the Syndrome by amphipathic carboxylates that may target both, HNF-4a as well as AMPK, and/or target tissues that do not express HNF-4a but still play a dominant role in the Syndrome phenotype, as described by applicant's claimed method, offer a comprehensive treatment mode that surpasses the performance of methods limited to modulating HNF-4a activity alone.

Therefore, the elements set forth in claims 29-32 of the subject application are clearly unobvious from the corresponding elements recited in any of claims 1-3 or 8 of the '653 patent. Applicant further notes that in the comparison of patented claim to pending claim required for obviousness-type double patenting, only individual claims of the patent may be considered. Thus, the claims of the patent may not be combined like prior art for this purpose. Only the specific combination of these elements as now recited provides the unexpected benefits associated with applicant's claimed invention. Accordingly, applicant maintains that claims 29-32 are patentably distinct over claims 1-3 and 8 of the '653 patent.

In view of the above remarks, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicant respectfully requests that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $225.00 fee for a two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

11/20/06

John P. White Date
Reg. No. 28,678